

REMARKS

Claims 1-41 are pending in the application. Claims 3, 5, 8-18, 24, 25, and 27-41 are currently withdrawn from consideration. Claims 1, 2, 4, 6, 7, 19, 20, 21, 22, 23, and 26 are currently under examination. Claims 1, 2, 4, 6, 7, 19, 20, 21, 22, 23, and 26 currently stand rejected. No claims are currently amended.

Applicants thank the Examiner for withdrawing prior rejections of Claims 1, 2, 4, 6, 7, 19, 20, 21, 22, and 26 under 35 USC §102(b) and 35 USC §103.

New Claim Rejections

Claim Rejections under 35 USC §103 over Müller et al., WO 97/01580, and Shu et al.

Claims 1, 2, 4, 6, 7, 19, 20, 21, 22, and 26 stand rejected under 35 U.S.C. §103 over Müller et al., as evidenced by WO 97/01580 in view of Shu et al. (1995). According to the Office Action (OA), Müller et al. discloses a multifunctional compound comprising fully functional heterodimers. It is admitted that Müller et al. does not disclose a non-immunoglobulin portion having receptor or ligand function. Shu et al. allegedly discloses making and using a non-immunoglobulin portion having receptor or ligand function. WO 97/10580 is cited as a supporting document. It is argued that, in light of the disclosures in Müller et al. and Shu et al., it would be obvious to make and use the claimed invention, and motivation is provided by the disclosure in Shu et al. that bringing IL-2 to a “site of interest” by antibody binding to a tumor antigen reduces “considerable systematic toxicity” (OA on page 6 at lines 19-22). Applicants traverse.

Prima facie obviousness

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. *See*, MPEP §§ 2142, 2143

No motivation to combine or modify the references

Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. MPEP §2143.01. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found

in the prior art, not in applicant's disclosure. MPEP §2143, citing *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991). Here, the claims recite multifunctional compounds (*i.e.*, heterodimers) having two polypeptide chains, wherein one polypeptide chain includes the constant CH1-domain of an immunoglobulin heavy chain and the other polypeptide chain includes the constant CL-domain of an immunoglobulin light chain, and the polypeptide chains further include, fused to the constant domains, at least two polypeptide functional domains having different receptor or ligand functions, wherein at least one of the functional domains includes a non-immunoglobulin portion having receptor or ligand function, and further wherein at least two of the different functional domains lack an intrinsic affinity for one another and the polypeptide chains are linked via the immunoglobulin constant domains.

Müller *et al.* discloses a heterodimeric "bispecific miniantibody" wherein one polypeptide chain includes a CH1-domain linked to VH and VL of an anti-EGF-R scFv fragment, and the other polypeptide chain includes a CL1-domain linked to VH and VL of an anti-CD2 scFv fragment. Shu *et al.* discloses a single-chain fusion protein SC Ig-IL-2, wherein the polypeptide chain includes heavy and light chain variable regions derived from the CC49 monoclonal antibody (anti-TAG-72 Fv), covalently linked CH2 and CH3 domains, and IL-2, where the carboxyl end of the light chain of the anti-TAG-72 Fv domain is covalently linked to CH2, and IL-2 covalently linked to the carboxyl end of the CH3 domain.

Neither Müller *et al.* nor Shu *et al.* contain a teaching, suggestion, or motivation to combine or modify the teachings of the cited references to produce the claimed invention. Limited to "bispecific miniantibodies," Müller *et al.* fails to teach or even suggest a non-immunoglobulin portion having receptor or ligand function as in the claimed invention. Shu *et al.*, limited to a single chain fusion protein containing CH2 and CH3, does not teach or even suggest using CL and CH1 domains, or heterodimer formation, much less using CL-CH1 as a heterodimerization domain, as in the claimed invention. Without a teaching, suggestion, or motivation to combine or modify the teachings of Müller *et al.* and Shu *et al.* to produce the claimed invention, no *prima facie* case of obviousness has been established.

Cited references do not teach the claimed invention.

To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. MPEP §2143.03, citing *In re Royka*, 180 USPQ 580 (CCPA 1974). Müller *et al.* and Shu *et al.* cannot be combined or modified to produce the claimed invention described above. Müller *et al.* allegedly discloses a multifunctional compound comprising fully functional heterodimers, but admittedly does not disclose a non-immunoglobulin portion having receptor or ligand function. Shu *et al.* allegedly discloses a

non-immunoglobulin portion having receptor or ligand function, but does not disclose the use of CH1 or CL or the formation of heterodimers via the CH1 and CL constant domains. Combining the bispecific miniantibodies of Müller *et al.*, with the single chain fusion protein and homodimer of Shu *et al.*, does not teach or suggest the claimed invention and therefore, no *prima facie* case of obviousness has been established.

Claim Rejections under 35 USC §103 over Müller et al., Shu et al., and Plückthun and Pack

Claims 1, 2, 4, 6, 7, 19, 20, 21, 22, and 26 stand rejected under 35 U.S.C. §103(a) over Müller *et al.* in view of Shu *et al.*, and further in view of Plückthun and Pack. According to the Office Action, Müller *et al.* discloses a multifunctional compound comprising two monomers, but admittedly does not disclose a non-immunoglobulin portion having receptor or ligand function, and does not teach using the upper hinge region of human IgG3. Shu *et al.* is cited for allegedly teaching making and using a non-immunoglobulin portion having receptor or ligand function. Plückthun and Pack is cited for allegedly disclosing the use of the upper hinge region from human IgG3.

It is argued that it would have been obvious to substitute the linkers of Müller *et al.* with the upper hinge region of human IgG3 taught by Plückthun and Pack, with an expectation of success because each reference allegedly teaches how to make each element of the claimed invention. It is further argued that motivation is provided by the disclosure in Plückthun and Pack that the human IgG3 upper hinge region increases flexibility and reduces immunogenicity, and further by the disclosure in Müller *et al.* that reducing immunogenicity is desirable.

The criteria for establishing a *prima facie* case of obviousness is presented above.

As discussed above, there is no motivation to combine Müller *et al.* and Shu *et al.* to make the claimed invention. Furthermore, the combination of Müller *et al.* and Shu *et al.* does not even teach the claimed invention. Substituting the linkers disclosed in Müller *et al.* with the upper hinge region of human IgG3 disclosed in Plückthun and Pack does not produce the claimed invention and fails to cure the deficiency of the rejection. We conclude that no *prima facie* case of obviousness has been established and the rejection under 35 USC §103 should be withdrawn.

CONCLUSION

Claims 1-41 are pending in the application. Claims 3, 5, 8-18, 24, 25, and 27-41 are currently withdrawn from consideration. Claims 1, 2, 4, 6, 7, 19, 20, 21, 22, 23, and 26 are currently under examination. Claims 1, 2, 4, 6, 7, 19, 20, 21, 22, 23, and 26 currently stand rejected. No listing of claims is included because no claims are amended. If requested, Applicants will gladly provide a listing of claims.

This paper is being submitted within two months of the mailing date of the outstanding final Office Action. Applicants request consideration of the arguments presented here be considered and speedy issuance of a notice of allowance.

Applicants believe no fees are due. If any fees are due, please charge any fees associated with the submission of this paper to Deposit Account Number 033975. The Commissioner for Patents is also authorized to credit any over payments to the above-referenced Deposit Account.

Respectfully submitted,

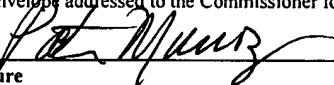
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CERTIFICATION UNDER 37 C.F.R. §§ 1.8 and/or 1.10*

I hereby certify that, on the date shown below, this paper (along with any paper referred to as being attached or enclosed) is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to the Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

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Signature

Patricia Munoz
(type or print name of person certifying)